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<110> Lorantis Ltd.

<120> Modulations of Notch signalling for use in Immunotherapy

<130> P011073US

<140> 10/764,415

<141> 2004-07-23

<150> GB0118153.6

<151> 2001-07-01

<150> GB0207930.9

<151> 2002-04-05

<150> GB0212283.6

<151> 2002-05-28

<150> GB0212282.8

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<170> PatentIn version 3.0

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<211> 43

<212> PRT

<213> Artificial

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Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys 35 40

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- <211> 43
- <212> PRT
- <213> Artificial
- <220>
- <223> DSL consensus
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- <221> MISC_FEATURE
- <222> (2)..(4)
- <223> X is any amino acid residue
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- <221> MISC_FEATURE
- <222> (5)..(6)
- <223> X is any aromatic amino acid residue
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- <222> (7)..(9)
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- <222> (15)..(15)
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- <222> (16)..(16)
- <223> X is any non polar amino acid residue
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- <222> (17)..(17)
- <223> X is any basic amino acid residue
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- <221> MISC_FEATURE
- <222> (18)..(19)
- <223> X is Asp, Asn, Glu or Gln
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- <222> (20)..(20)
- <223> X is any amino acid residue
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Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys 35 40
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<213> Artificial
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<222> (35)..(36)

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<222> (39)..(39)

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Cys Xaa Xaa Xaa Tyr Tyr Xaa Xaa Xaa Cys Xaa Xaa Xaa Cys Arg Pro 1 5 10 15

Arg Xaa Asp Xaa Phe Gly His Xaa Xaa Cys Xaa Xaa Xaa Gly Xaa Xaa 20 25 30

Xaa Cys Xaa Xaa Gly Trp Xaa Gly Xaa Xaa Cys 35

<210> 4

<211> 175

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<222> (57)..(66)

<223> Any of residues 57-66 may be present or absent

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<222> (68)..(137)

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- <222> (69)..(137)
- <223> Any of residues 69 137 may be present or absent
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- <222> (139)..(144)
- <223> X is any amino acid
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- <221> VARIANT
- <222> (140)..(144)
- <223> Any of residues 140 144 may be present or absent
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- <221> MISC_FEATURE
- <222> (146)..(147)
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- <222> (150)..(170)
- <223> X is any amino acid
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- <221> VARIANT
- <222> (150)..(170)
- <223> Any of residues 150-170 may be present or absent
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- <222> (172)..(173)

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<222> (175)..(175)

<223> X is any amino acid

<400> 4

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Xaa Xaa Cys Xaa 165 170 175

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<213> Artificial

<220>

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<400> 5

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<400> 6
                                                                    20
ccatccaatc ggtagtagcg
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                                                                    20
ggtgctgata acagcggaat
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<211> 20
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<213> Artificial
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<400> 8
                                                                    20
atttttggaa tccttcacgc
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<211> 26
<212> DNA
<213> Artificial
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                                                                     26
gatctggggg gctataaaag ggggta
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acccccgat attttccccc attcga
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gatcccgact cgtgggaaaa tgggcggaag ggcaccgtgg gaaaatagta
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ggctgcacct gctgggtctg c
                                                                     21
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aaaggattca ccatggcacg caagcgccgg cgcagt
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<223> Expression product

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Gly Phe Lys Val Ser Glu Ala Ser Lys Lys Lys Arg Arg Glu Pro Leu 20 25 30

Gly Glu Asp Ser Val Gly Leu Lys Pro Leu Lys Asn Ala Ser Asp Gly 35 40 45

Ala Leu Met Asp Asp Asn Gln Asn Glu Trp Gly Asp Glu Asp Leu Glu 50 60

Thr Lys Lys Phe Arg Phe Glu Glu Pro Val Val Leu Pro Asp Leu Asp 65 70 75 80

Asp Gln Thr Asp His Arg Gln Trp Thr Gln Gln His Leu Asp Ala Ala 85 90 95

Asp Leu Arg Met Ser Ala Met Ala Pro Thr Pro Pro Gln Gly Glu Val $100 \hspace{1cm} 105 \hspace{1cm} 110$

Asp Ala Asp Cys Met Asp Val Asn Val Arg Gly Pro Asp Gly Phe Thr 115 120 125

Pro Leu Met Ile Ala Ser Cys Ser Gly Gly Gly Leu Glu Thr Gly Asn 130 135 140

Ser Glu Glu Glu Asp Ala Pro Ala Val Ile Ser Asp Phe Ile Tyr 145 150 155 160

Gln Gly Ala Ser Leu His Asn Gln Thr Asp Arg Thr Gly Glu Thr Ala 165 170 175

Leu His Leu Ala Ala Arg Tyr Ser Arg Ser Asp Ala Ala Lys Arg Leu 180 185 190

Leu Glu Ala Ser Ala Asp Ala Asn Ile Gln Asp Asn Met Gly Arg Thr 195 200 205

Pro Leu His Ala Ala Val Ser Ala Asp Ala Gln Gly Val Phe Gln Ile 210 220

Leu Ile Arg Asn Arg Ala Thr Asp Leu Asp Ala Arg Met His Asp Gly 235 230 240

Thr Thr Pro Leu Ile Leu Ala Ala Arg Leu Ala Val Glu Gly Met Leu 245 250 255 Glu Asp Leu Ile Asn Ser His Ala Asp Val Asn Ala Val Asp Asp Leu 260 265 270 Gly Lys Ser Ala Leu His Trp Ala Ala Ala Val Asn Asn Val Asp Ala 275 280 285 Ala Val Val Leu Leu Lys Asn Gly Ala Asn Lys Asp Met Gln Asn Asn 290 295 300 Arg Glu Glu Thr Pro Leu Phe Leu Ala Ala Arg Glu Gly Ser Tyr Glu 305 310 315 320 Thr Ala Lys Val Leu Leu Asp His Phe Ala Asn Arg Asp Ile Thr Asp 325 330 335 His Met Asp Arg Leu Pro Arg Asp Ile Ala Gln Glu Arg Met His His 340 345 350 Asp Ile Val Arg Leu Leu Asp Glu Tyr Asn Leu Val Arg Ser Pro Gln 355 360 365 Leu His Gly Ala Pro Leu Gly Gly Thr Pro Thr Leu Ser Pro Pro Leu 370 380 Cys Ser Pro Asn Gly Tyr Leu Gly Ser Leu Lys Pro Gly Val Gln Gly 385 390 395 400 Lys Lys Val Arg Lys Pro Ser Ser Lys Gly Leu Ala Cys Gly Ser Lys
405 410 415 Glu Ala Lys Asp Leu Lys Ala Arg Arg Lys Lys Ser Gln Asp Gly Lys 420 425 430 Gly Cys Leu Leu Asp Ser Ser Gly Met Leu Ser Pro Val Asp Ser Leu 435 440 445 Glu Ser Pro His Gly Tyr Leu Ser Asp Val Ala Ser Pro Pro Leu Leu 450 455 460 Pro Ser Pro Phe Gln Gln Ser Pro Ser Val Pro Leu Asn His Leu Pro 465 470 475 480 Gly Met Pro Asp Thr His Leu Gly Ile Gly His Leu Asn Val Ala Ala 485 490 495 Lys Pro Glu Met Ala Ala Leu Gly Gly Gly Gly Arg Leu Ala Phe Glu 500 510 Thr Gly Pro Pro Arg Leu Ser His Leu Pro Val Ala Ser Gly Thr Ser 515 520 525 Thr Val Leu Gly Ser Ser Ser Gly Gly Ala Leu Asn Phe Thr Val Gly 530 540 Gly Ser Thr Ser Leu Asn Gly Gln Cys Glu Trp Leu Ser Arg Leu Gln 545 555 560 Ser Gly Met Val Pro Asn Gln Tyr Asn Pro Leu Arg Gly Ser Val Ala 565 570 575 Pro Gly Pro Leu Ser Thr Gln Ala Pro Ser Leu Gln His Gly Met Val

580 585 590

Gly Pro Leu His Ser Ser Leu Ala Ala Ser Ala Leu Ser Gln Met Met 600 Ser Tyr Gln Gly Leu Pro Ser Thr Arg Leu Ala Thr Gln Pro His Leu 610 620 Val Gln Thr Gln Gln Val Gln Pro Gln Asn Leu Gln Met Gln Gln 625 635 640 Asn Leu Gln Pro Ala Asn Ile Gln Gln Gln Gln Ser Leu Gln Pro Pro 645 650 655 Pro Pro Pro Gln Pro His Leu Gly Val Ser Ser Ala Ala Ser Gly 660 665 670 His Leu Gly Arg Ser Phe Leu Ser Gly Glu Pro Ser Gln Ala Asp Val 675 680 685 Gln Pro Leu Gly Pro Ser Ser Leu Ala Val His Thr Ile Leu Pro Gln 690 695 700 Glu Ser Pro Ala Leu Pro Thr Ser Leu Pro Ser Ser Leu Val Pro Pro 705 710 715 720 Val Thr Ala Ala Gln Phe Leu Thr Pro Pro Ser Gln His Ser Tyr Ser 725 730 735 Ser Pro Val Asp Asn Thr Pro Ser His Gln Leu Gln Val Pro Glu His 740 745 750 Pro Phe Leu Thr Pro Ser Pro Glu Ser Pro Asp Gln Trp Ser Ser Ser 755 760 765 Ser Pro His Ser Asn Val Ser Asp Trp Ser Glu Gly Val Ser Ser Pro 770 780 Pro Thr Ser Met Gln Ser Gln Ile Ala Arg Ile Pro Glu Ala Phe Lys 785 790 795 800 <210> 18 <211> 63

<212> PRT

<213> Drosophila sp.

<400> 18

Trp Lys Thr Asn Lys Ser Glu Ser Gln Tyr Thr Ser Leu Glu Tyr Asp 10 Phe Arg Val Thr Cys Asp Leu Asn Tyr Tyr Gly Ser Gly Cys Ala Lys 20 Phe Cys Arg Pro Arg Asp Asp Ser Phe Gly His Ser Thr Cys Ser Glu Thr Gly Glu Ile Ile Cys Leu Thr Gly Trp Gln Gly Asp Tyr Cys 60

<210> 19

<211> 63

<212> PRT

<213> Homo sapiens

<400> 19

Trp Ser Gln Asp Leu His Ser Ser Gly Arg Thr Asp Leu Lys Tyr Ser 10 15

Tyr Arg Phe Val Cys Asp Glu His Tyr Tyr Gly Glu Gly Cys Ser Val 20 25 30

Phe Cys Arg Pro Arg Asp Asp Ala Phe Gly His Phe Thr Cys Gly Glu 35 40 45

Arg Gly Glu Lys Val Cys Asn Pro Gly Trp Lys Gly Pro Tyr Cys 50 55 60

<210> 20

<211> 63

<212> PRT

<213> Mus musculus

<400> 20

Trp Ser Gln Asp Leu His Ser Ser Gly Arg Thr Asp Leu Arg Tyr Ser $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$

Tyr Arg Phe Val Cys Asp Glu His Tyr Tyr Gly Glu Gly Cys Ser Val 20 25 30

Phe Cys Arg Pro Arg Asp Asp Ala Phe Gly His Phe Thr Cys Gly Asp 35 40 45

Arg Gly Glu Lys Met Cys Asp Pro Gly Trp Lys Gly Gln Tyr Cys 50 60

<210> 21

<211> 63

<212> PRT

<213> Rattus rattus

<400> 21

Trp Ser Gln Asp Leu His Ser Ser Gly Arg Thr Asp Leu Arg Tyr Ser 10 15

Tyr Arg Phe Val Cys Asp Glu His Tyr Tyr Gly Glu Gly Cys Ser Val 20 25 30

Phe Cys Arg Pro Arg Asp Asp Ala Phe Gly His Phe Thr Cys Gly Glu 35 40 45

Arg Gly Glu Lys Met Cys Asp Pro Gly Trp Lys Gly Gln Tyr Cys 50 60

<210> 22

<211> 63

<212> PRT

<213> Mus musculus

<400> 22

Trp Arg Thr Asp Glu Gln Asn Asp Thr Leu Thr Arg Leu Ser Tyr Ser 10 15

Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Glu Ser Cys Ser Arg 20 25 30

Leu Cys Lys Lys Arg Asp Asp His Phe Gly His Tyr Glu Cys Gln Pro 35 40 45

Asp Gly Ser Leu Ser Cys Leu Pro Gly Trp Thr Gly Lys Tyr Cys 50 55 60

<210> 23

<211> 63

<212> PRT

<213> Homo sapiens

<400> 23

Trp Leu Leu Asp Glu Gln Thr Ser Thr Leu Thr Arg Leu Arg Tyr Ser 10 15

Tyr Arg Val Ile Cys Ser Asp Asn Tyr Tyr Gly Asp Asn Cys Ser Arg

Leu Cys Lys Lys Arg Asn Asp His Phe Gly His Tyr Val Cys Gln Pro 35 40 45

Asp Gly Asn Leu Ser Cys Leu Pro Gly Trp Thr Gly Glu Tyr Cys 50 55 60

<210> 24

<211> 63

<212> PRT

<213> Rattus rattus

<400> 24

Trp Gln Thr Leu Lys Gln Asn Thr Gly Ile Ala His Phe Glu Tyr Gln
10 15

Ile Arg Val Thr Cys Asp Asp His Tyr Tyr Gly Phe Gly Cys Asn Lys 20 25 30

Phe Cys Arg Pro Arg Asp Asp Phe Phe Gly His Tyr Ala Cys Asp Gln 35 40 45

Asn Gly Asn Lys Thr Cys Met Glu Gly Trp Met Gly Pro Glu Cys 50 55 60

<210> 25

<211> 63

<212> PRT

<213> Mus musculus

<400> 25

Trp Gln Thr Leu Lys Gln Asn Thr Gly Ile Ala His Phe Glu Tyr Gln
10 15

Ile Arg Val Thr Cys Asp Asp His Tyr Tyr Gly Phe Gly Cys Asn Lys $20 \hspace{1cm} 25 \hspace{1cm} 30$

Phe Cys Arg Pro Arg Asp Asp Phe Phe Gly His Tyr Ala Cys Asp Gln 35 40 45

Asn Gly Asn Lys Thr Cys Met Glu Gly Trp Met Gly Pro Asp Cys 50 55 60

<210> 26

<211> 63

<212> PRT

<213> Homo sapiens

<400> 26

Trp Gln Thr Leu Lys Gln Asn Thr Gly Val Ala His Phe Glu Tyr Gln
10 15

Ile Arg Val Thr Cys Asp Asp Tyr Tyr Tyr Gly Phe Gly Cys Asn Lys 20 25 30

Phe Cys Arg Pro Arg Asp Asp Phe Phe Gly His Tyr Ala Cys Asp Gln 35 40 45

Asn Gly Asn Lys Thr Cys Met Glu Gly Trp Met Gly Arg Glu Cys 50 60

<210> 27

<211> 63

<212> PRT

<213> Gallus sp.

<400> 27

Trp Gln Thr Leu Lys His Asn Thr Gly Ala Ala His Phe Glu Tyr Gln 10 15

Ile Arg Val Thr Cys Ala Glu His Tyr Tyr Gly Phe Gly Cys Asn Lys 20 25 30

Phe Cys Arg Pro Arg Asp Asp Phe Phe Thr His His Thr Cys Asp Gln 35 40 45

Asn Gly Asn Lys Thr Cys Leu Glu Gly Trp Thr Gly Pro Glu Cys 50 55 60

<210> 28

<211> 63

<212> PRT

<213> Gallus sp.

<400> 28

Trp Lys Thr Leu Gln Phe Asn Gly Pro Val Ala Asn Phe Glu Val Gln $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$

Ile Arg Val Lys Cys Asp Glu Asn Tyr Tyr Ser Ala Leu Cys Asn Lys 20 25 30

Phe Cys Gly Pro Arg Asp Asp Phe Val Gly His Tyr Thr Cys Asp Gln 35 40 45

Asn Gly Asn Lys Ala Cys Met Glu Gly Trp Met Gly Glu Glu Cys 50 55 60

<210> 29

<211> 63

<212> PRT

<213> Mus musculus

<400> 29

Trp Lys Ser Leu His Phe Ser Gly His Val Ala His Leu Glu Leu Gln
5 10 15

Ile Arg Val Arg Cys Asp Glu Asn Tyr Tyr Ser Ala Thr Cys Asn Lys 20 25 30

Phe Cys Arg Pro Arg Asn Asp Phe Phe Gly His Tyr Thr Cys Asp Gln 35 40 45

Tyr Gly Asn Lys Ala Cys Met Asp Gly Trp Met Gly Lys Glu Cys 50 55 60 30 <210> 63 <211> <212> **PRT** <213> Homo sapiens <400> 30 Trp Lys Ser Leu His Phe Ser Gly His Val Ala His Leu Glu Leu Gln 1 5 10 15 Ile Arg Val Arg Cys Asp Glu Asn Tyr Tyr Ser Ala Thr Cys Asn Lys 20 25 30 Phe Cys Arg Pro Arg Asn Asp Phe Phe Gly His Tyr Thr Cys Asp Gln 35 40 45 Tyr Gly Asn Lys Ala Cys Met Asp Gly Trp Met Gly Lys Glu Cys 50 55 60<210> 31 <211> 63 <212> PRT <213> Rattus rattus <400> 31 Trp Lys Ser Leu His Phe Ser Gly His Val Ala His Leu Glu Leu Gln 1 5 10 15 Ile Arg Val Arg Cys Asp Glu Asn Tyr Tyr Ser Ala Thr Cys Asn Lys 20 25 30 Phe Cys Arg Pro Arg Asn Asp Phe Phe Gly His Tyr Thr Cys Asp Gln 35 40 45 Tyr Gly Asn Lys Ala Cys Met Asp Gly Trp Met Gly Lys Glu Cys 50 55 60 <210> 32 63 <211> <212> **PRT** <213> Homo sapiens <400>

Trp Lys Ser Leu His Phe Ser Gly His Val Ala His Leu Glu Leu Gln

5 10 15

Ile Arg Val Arg Cys Asp Glu Asn Tyr Tyr Ser Ala Thr Cys Asn Lys 20 25 30

Phe Cys Arg Pro Arg Asn Asp Phe Phe Gly His Tyr Thr Cys Asp Gln 35 40 45

Tyr Gly Asn Lys Ala Cys Met Asp Gly Trp Met Gly Lys Glu Cys 50 55 60

<210> 33

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<211> 63

<212> PRT

<213> Drosophila melanogaster

<400> 33

Trp Lys Thr Leu Asp His Ile Gly Arg Asn Ala Arg Ile Thr Tyr Arg
1 10 15

Val Arg Val Gln Cys Ala Val Thr Tyr Tyr Asn Thr Thr Cys Thr Thr 20 25 30

Phe Cys Arg Pro Arg Asp Asp Gln Phe Gly His Tyr Ala Cys Gly Ser 35 40 45

Glu Gly Gln Lys Leu Cys Leu Asn Gly Trp Gln Gly Val Asn Cys 50 55 60

<210> 34

<211> 723

<212> PRT

<213> Homo sapiens

<400> 34

Met Gly Ser Arg Cys Ala Leu Ala Leu Ala Val Leu Ser Ala Leu Leu $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$

Cys Gln Val Trp Ser Ser Gly Val Phe Glu Leu Lys Leu Gln Glu Phe 20 25 30

Val Asn Lys Lys Gly Leu Leu Gly Asn Arg Asn Cys Cys Arg Gly Gly 35 40 45

Ala Gly Pro Pro Cys Ala Cys Arg Thr Phe Phe Arg Val Cys Leu 50 60

Lys His Tyr Gln Ala Ser Val Ser Pro Glu Pro Pro Cys Thr Tyr Gly 65 70 75 80

Ser Ala Val Thr Pro Val Leu Gly Val Asp Ser Phe Ser Leu Pro Asp 85 90 95

Gly Gly Gly Ala Asp Ser Ala Phe Ser Asn Pro Ile Arg Phe Pro Phe $100 \hspace{1cm} 105 \hspace{1cm} 110$ Gly Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile Glu Ala Leu His 115 120 125 Thr Asp Ser Pro Asp Asp Leu Ala Thr Glu Asn Pro Glu Arg Leu Ile 130 135 140 Ser Arg Leu Ala Thr Gln Arg His Leu Thr Val Gly Glu Glu Trp Ser 145 150 155 160 Gln Asp Leu His Ser Ser Gly Arg Thr Asp Leu Lys Tyr Ser Tyr Arg 165 170 175 Phe Val Cys Asp Glu His Tyr Tyr Gly Glu Gly Cys Ser Val Phe Cys 180 185 190 Arg Pro Arg Asp Asp Ala Phe Gly His Phe Thr Cys Gly Glu Arg Gly 195 200 205 Glu Lys Val Cys Asn Pro Gly Trp Lys Gly Pro Tyr Cys Thr Glu Pro 210 220 Ile Cys Leu Pro Gly Cys Asp Glu Gln His Gly Phe Cys Asp Lys Pro 225 230 235 240 Gly Glu Cys Lys Cys Arg Val Gly Trp Gln Gly Arg Tyr Cys Asp Glu 245 250 255 Cys Ile Arg Tyr Pro Gly Cys Leu His Gly Thr Cys Gln Gln Pro Trp 260 265 270 Gln Cys Asn Cys Gln Glu Gly Trp Gly Gly Leu Phe Cys Asn Gln Asp 275 280 285 Leu Asn Tyr Cys Thr His His Lys Pro Cys Lys Asn Gly Ala Thr Cys 290 295 300 Thr Asn Thr Gly Gln Gly Ser Tyr Thr Cys Ser Cys Arg Pro Gly Tyr 305 310 315 320 Thr Gly Ala Thr Cys Glu Leu Gly Ile Asp Glu Cys Asp Pro Ser Pro 325 330 335 Cys Lys Asn Gly Gly Ser Cys Thr Asp Leu Glu Asn Ser Tyr Ser Cys 340 345 350 Thr Cys Pro Pro Gly Phe Tyr Gly Lys Ile Cys Glu Leu Ser Ala Met 355 360 365 Thr Cys Ala Asp Gly Pro Cys Phe Asn Gly Gly Arg Cys Ser Asp Ser 370 380 Pro Asp Gly Gly Tyr Ser Cys Arg Cys Pro Val Gly Tyr Ser Gly Phe 385 390 395 400 Asn Cys Glu Lys Lys Ile Asp Tyr Cys Ser Ser Ser Pro Cys Ser Asn 405 410 415Gly Ala Lys Cys Val Asp Leu Gly Asp Ala Tyr Leu Cys Arg Cys Gln 420 425 430 Ala Gly Phe Ser Gly Arg His Cys Asp Asp Asp Val Asp Asp Cys Ala 435 440 445

Ser Pro Cys Ala Asn Gly Gly Thr Cys Arg Asp Gly Val Asn Asp 450 460 Phe Ser Cys Thr Cys Pro Pro Gly Tyr Thr Gly Arg Asn Cys Ser Ala 465 470 475 480 Pro Val Ser Arg Cys Glu His Ala Pro Cys His Asn Gly Ala Thr Cys 485 490 495 His Glu Arg Gly His Gly Tyr Val Cys Glu Cys Ala Arg Gly Tyr Gly 500 505 510 Gly Pro Asn Cys Gln Phe Leu Leu Pro Glu Leu Pro Pro Gly Pro Ala 515 520 525 Val Val Asp Leu Thr Glu Lys Leu Glu Gly Gln Gly Gly Pro Phe Pro 530 540 Trp Val Ala Val Cys Ala Gly Val Ile Leu Val Leu Met Leu Leu Leu 545 550 555 560 Gly Cys Ala Ala Val Val Cys Val Arg Leu Arg Leu Gln Lys His 565 570 575 Arg Pro Pro Ala Asp Pro Cys Arg Gly Glu Thr Glu Thr Met Asn Asn 580 585 590 Leu Ala Asn Cys Gln Arg Glu Lys Asp Ile Ser Val Ser Ile Ile Gly 595 600 605 Ala Thr Gln Ile Lys Asn Thr Asn Lys Lys Ala Asp Phe His Gly Asp 610 620 His Ser Ala Asp Lys Asn Gly Phe Lys Ala Arg Tyr Pro Ala Val Asp 625 630 635 640 Tyr Asn Leu Val Gln Asp Leu Lys Gly Asp Asp Thr Ala Val Arg Asp 645 650 655 Ala His Ser Lys Arg Asp Thr Lys Cys Gln Pro Gln Gly Ser Ser Gly 660 665 670 Glu Glu Lys Gly Thr Pro Thr Thr Leu Arg Gly Glu Ala Ser Glu 675 680 685 Arg Lys Arg Pro Asp Ser Gly Cys Ser Thr Ser Lys Asp Thr Lys Tyr 690 695 700 Gln Ser Val Tyr Val Ile Ser Glu Glu Lys Asp Glu Cys Val Ile Ala 705 710 715 720 Thr Glu Val

<210> 35

<211> 618

<212> PRT

<213> Homo sapiens

Met Val Ser Pro Arg Met Ser Gly Leu Leu Ser Gln Thr Val Ile Leu 1 5 10 15 Ala Leu Ile Phe Leu Pro Gln Thr Arg Pro Ala Gly Val Phe Glu Leu 20 25 30 Gln Ile His Ser Phe Gly Pro Gly Pro Gly Pro Gly Ala Pro Arg Ser 35 40 45 Pro Cys Ser Ala Arg Leu Pro Cys Arg Leu Phe Phe Arg Val Cys Leu 50 60 Lys Pro Gly Leu Ser Glu Glu Ala Ala Glu Ser Pro Cys Ala Leu Gly 65 70 75 80 Ala Ala Leu Ser Ala Arg Gly Pro Val Tyr Thr Glu Gln Pro Gly Ala 85 90 95 Pro Ala Pro Asp Leu Pro Leu Pro Asp Gly Leu Leu Gl
n Val Pro Phe 100 $\,$ 110 Arg Asp Ala Trp Pro Gly Thr Phe Ser Phe Ile Ile Glu Thr Trp Arg 115 120 125 Glu Glu Leu Gly Asp Gln Ile Gly Gly Pro Ala Trp Ser Leu Leu Ala 130 135 140 Arg Val Ala Gly Arg Arg Leu Ala Ala Gly Gly Pro Trp Ala Arg 145 150 155 160 Asp Ile Gln Arg Ala Gly Ala Trp Glu Leu Arg Phe Ser Tyr Arg Ala 165 170 175 Arg Cys Glu Pro Pro Ala Val Gly Thr Ala Cys Thr Arg Leu Cys Arg 180 185 190 Pro Arg Ser Ala Pro Ser Arg Cys Gly Pro Gly Leu Arg Pro Cys Ala 195 200 205 Pro Leu Glu Asp Glu Cys Glu Ala Pro Leu Val Cys Arg Ala Gly Cys 210 220 Ser Pro Glu His Gly Phe Cys Glu Gln Pro Gly Glu Cys Arg Cys Leu 225 230 235 240 Glu Gly Trp Thr Gly Pro Leu Cys Thr Val Pro Val Ser Thr Ser Ser 245 250 255 Cys Leu Ser Pro Arg Gly Pro Ser Ser Ala Thr Thr Gly Cys Leu Val 260 265 270 Pro Gly Pro Cys Asp Gly Asn Pro Cys Ala Asn Gly Gly Ser 275 280 285 Cys Ser Glu Thr Pro Arg Ser Phe Glu Cys Thr Cys Pro Arg Gly Phe 290 295 300 Tyr Gly Leu Arg Cys Glu Val Ser Gly Val Thr Cys Ala Asp Gly Pro 305 310 315 320 Cys Phe Asn Gly Gly Leu Cys Val Gly Gly Ala Asp Pro Asp Ser Ala 325 330 335

Tyr Ile Cys His Cys Pro Pro Gly Phe Gln Gly Ser Asn Cys Glu Lys 340 345 350 Arg Val Asp Arg Cys Ser Leu Gln Pro Cys Arg Asn Gly Gly Leu Cys 355 360 365 Leu Asp Leu Gly His Ala Leu Arg Cys Arg Cys Arg Ala Gly Phe Ala 370 380 Gly Pro Arg Cys Glu His Asp Leu Asp Asp Cys Ala Gly Arg Ala Cys 385 390 395 400 Ala Asn Gly Gly Thr Cys Val Glu Gly Gly Gly Ala His Arg Cys Ser 405 410 415 Cys Ala Leu Gly Phe Gly Gly Arg Asp Cys Arg Glu Arg Ala Asp Pro 420 425 430 Cys Ala Ala Arg Pro Cys Ala His Gly Gly Arg Cys Tyr Ala His Phe 435 440 445 Ser Gly Leu Val Cys Ala Cys Ala Pro Gly Tyr Met Gly Ala Arg Cys 450 460 Glu Phe Pro Val His Pro Asp Gly Ala Ser Ala Leu Pro Ala Ala Pro 465 470 475 480 Pro Gly Leu Arg Pro Gly Asp Pro Gln Arg Tyr Leu Leu Pro Pro Ala 485 490 495 Leu Gly Leu Leu Val Ala Ala Gly Val Ala Gly Ala Ala Leu Leu Leu 500 510 Val His Val Arg Arg Arg Gly His Ser Gln Asp Ala Gly Ser Arg Leu 515 520 525 Leu Ala Gly Thr Pro Glu Pro Ser Val His Ala Leu Pro Asp Ala Leu 530 535 540 Asn Asn Leu Arg Thr Gln Glu Gly Ser Gly Asp Gly Pro Ser Ser Ser 545 550 555 Val Asp Trp Asn Arg Pro Glu Asp Val Asp Pro Gln Gly Ile Tyr Val 565 570 575 Ile Ser Ala Pro Ser Ile Tyr Ala Arg Glu Val Ala Thr Pro Leu Phe 580 585 590 Pro Pro Leu His Thr Gly Arg Ala Gly Gln Arg Gln His Leu Leu Phe 595 600 605 Pro Tyr Pro Ser Ser Ile Leu Ser Val Lys 610 615

<210> 36

<211> 685

<212> PRT

<213> Homo sapiens

Met Ala Ala Ser Arg Ser Ala Ser Gly Trp Ala Leu Leu Leu 1 5 10 15 Val Ala Leu Trp Gln Gln Arg Ala Ala Gly Ser Gly Val Phe Gln Leu 20 25 30 Gln Leu Gln Glu Phe Ile Asn Glu Arg Gly Val Leu Ala Ser Gly Arg 35 40 45Pro Cys Glu Pro Gly Cys Arg Thr Phe Phe Arg Val Cys Leu Lys His 50 55 Phe Gln Ala Val Val Ser Pro Gly Pro Cys Thr Phe Gly Thr Val Ser 65 70 75 80 Thr Pro Val Leu Gly Thr Asn Ser Phe Ala Val Arg Asp Asp Ser Ser 85 90 95 Gly Gly Gly Arg Asn Pro Leu Gln Leu Pro Phe Asn Phe Thr Trp Pro $100 \hspace{1cm} 105 \hspace{1cm} 110$ Gly Thr Phe Ser Leu Ile Ile Glu Ala Trp His Ala Pro Gly Asp Asp 115 120 125 Leu Arg Pro Glu Ala Leu Pro Pro Asp Ala Leu Ile Ser Lys Ile Ala 130 135 140 Ile Gln Gly Ser Leu Ala Val Gly Gln Asn Trp Leu Leu Asp Glu Gln 145 150 155 160 Thr Ser Thr Leu Thr Arg Leu Arg Tyr Ser Tyr Arg Val Ile Cys Ser 165 170 175 Asp Asn Tyr Tyr Gly Asp Asn Cys Ser Arg Leu Cys Lys Lys Arg Asn 180 185 190 Asp His Phe Gly His Tyr Val Cys Gln Pro Asp Gly Asn Leu Ser Cys 195 200 205 Leu Pro Gly Trp Thr Gly Glu Tyr Cys Gln Gln Pro Ile Cys Leu Ser 210 220 Gly Cys His Glu Gln Asn Gly Tyr Cys Ser Lys Pro Ala Glu Cys Leu 225 230 235 240 Cys Arg Pro Gly Trp Gln Gly Arg Leu Cys Asn Glu Cys Ile Pro His 245 250 255 Asn Gly Cys Arg His Gly Thr Cys Ser Thr Pro Trp Gln Cys Thr Cys 260 265 270 Asp Glu Gly Trp Gly Gly Leu Phe Cys Asp Gln Asp Leu Asn Tyr Cys 275 280 285 Thr His His Ser Pro Cys Lys Asn Gly Ala Thr Cys Ser Asn Ser Gly 290 295 300 Gln Arg Ser Tyr Thr Cys Thr Cys Arg Pro Gly Tyr Thr Gly Val Asp 305 310 315 320 Cys Glu Leu Glu Leu Ser Glu Cys Asp Ser Asn Pro Cys Arg Asn Gly 325 330 335 Gly Ser Cys Lys Asp Gln Glu Asp Gly Tyr His Cys Leu Cys Pro Pro

Gly Tyr Tyr Gly Leu His Cys Glu His Ser Thr Leu Ser Cys Ala Asp 355 360 365 Pro Cys Phe Asn Gly Gly Ser Cys Arg Glu Arg Asn Gln Gly Ala 370 380 Asn Tyr Ala Cys Glu Cys Pro Pro Asn Phe Thr Gly Ser Asn Cys Glu 385 390 395 400 Lys Lys Val Asp Arg Cys Thr Ser Asn Pro Cys Ala Asn Gly Gln 405 410 415 Cys Leu Asn Arg Gly Pro Ser Arg Met Cys Arg Cys Arg Pro Gly Phe 420 430 Thr Gly Thr Tyr Cys Glu Leu His Val Ser Asp Cys Ala Arg Asn Pro 435 440 445 Cys Ala His Gly Gly Thr Cys His Asp Leu Glu Asn Gly Leu Met Cys 450 460 Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg Cys Glu Val Arg Thr Ser 465 470 475 480 Ile Asp Ala Cys Ala Ser Ser Pro Cys Phe Asn Arg Ala Thr Cys Tyr 485 490 495 Thr Asp Leu Ser Thr Asp Thr Phe Val Cys Asn Cys Pro Tyr Gly Phe 500 510 Val Gly Ser Arg Cys Glu Phe Pro Val Gly Leu Pro Pro Ser Phe Pro 515 520 525 Trp Val Ala Val Ser Leu Gly Val Gly Leu Ala Val Leu Leu Val Leu 530 540 Leu Gly Met Val Ala Val Ala Val Arg Gln Leu Arg Leu Arg Arg Pro 545 550 560 Asp Asp Gly Ser Arg Glu Ala Met Asn Asn Leu Ser Asp Phe Gln Lys 565 570 575 Asp Asn Leu Ile Pro Ala Ala Gln Leu Lys Asn Thr Asn Gln Lys Lys 580 585 590 Glu Leu Glu Val Asp Cys Gly Leu Asp Lys Ser Asn Cys Gly Lys Gln 595 600 605 Gln Asn His Thr Leu Asp Tyr Asn Leu Ala Pro Gly Pro Leu Gly Arg 610 615 620 Gly Thr Met Pro Gly Lys Phe Pro His Ser Asp Lys Ser Leu Gly Glu 625 635 640 Lys Ala Pro Leu Arg Leu His Ser Glu Lys Pro Glu Cys Arg Ile Ser 645 650 655 Ala Ile Cys Ser Pro Arg Asp Ser Met Tyr Gln Ser Val Cys Leu Ile 660 665 670 Ser Glu Glu Arg Asn Glu Cys Val Ile Ala Thr Glu Val 675 680 685

<210> 37

<211> 1218

<212> PRT

<213> Homo sapiens

<400> 37

Met Arg Ser Pro Arg Thr Arg Gly Arg Ser Gly Arg Pro Leu Ser Leu $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$ Leu Leu Ala Leu Leu Cys Ala Leu Arg Ala Lys Val Cys Gly Ala Ser 20 25 30 Gly Gln Phe Glu Leu Glu Ile Leu Ser Met Gln Asn Val Asn Gly Glu 35 40 45 Leu Gln Asn Gly Asn Cys Cys Gly Gly Ala Arg Asn Pro Gly Asp Arg 50 55 60 Lys Cys Thr Arg Asp Glu Cys Asp Thr Tyr Phe Lys Val Cys Leu Lys 65 70 75 80 Glu Tyr Gln Ser Arg Val Thr Ala Gly Gly Pro Cys Ser Phe Gly Ser 85 90 95 Gly Ser Thr Pro Val Ile Gly Gly Asn Thr Phe Asn Leu Lys Ala Ser 100 105 110Arg Gly Asn Asp Arg Asn Arg Ile Val Leu Pro Phe Ser Phe Ala Trp 115 120 125 Pro Arg Ser Tyr Thr Leu Leu Val Glu Ala Trp Asp Ser Ser Asn Asp 130 135 140 Thr Val Gln Pro Asp Ser Ile Ile Glu Lys Ala Ser His Ser Gly Met 145 150 155 160 Ile Asn Pro Ser Arg Gln Trp Gln Thr Leu Lys Gln Asn Thr Gly Val 165 170 175 Ala His Phe Glu Tyr Gln Ile Arg Val Thr Cys Asp Asp Tyr Tyr Tyr 180 185 190 Gly Phe Gly Cys Asn Lys Phe Cys Arg Pro Arg Asp Asp Phe Phe Gly 200 205 His Tyr Ala Cys Asp Gln Asn Gly Asn Lys Thr Cys Met Glu Gly Trp 210 215 220 Met Gly Pro Glu Cys Asn Arg Ala Ile Cys Arg Gln Gly Cys Ser Pro 225 230 235 240 Lys His Gly Ser Cys Lys Leu Pro Gly Asp Cys Arg Cys Gln Tyr Gly 245 250 255 Trp Gln Gly Leu Tyr Cys Asp Lys Cys Ile Pro His Pro Gly Cys Val 260 265 270 His Gly Ile Cys Asn Glu Pro Trp Gln Cys Leu Cys Glu Thr Asn Trp 275 280 285

Gly Gln Leu Cys Asp Lys Asp Leu Asn Tyr Cys Gly Thr His Gln 290 295 300 Pro Cys Leu Asn Gly Gly Thr Cys Ser Asn Thr Gly Pro Asp Lys Tyr 305 310 315 320 Gln Cys Ser Cys Pro Glu Gly Tyr Ser Gly Pro Asn Cys Glu Ile Ala 325 330 335 Glu His Ala Cys Leu Ser Asp Pro Cys His Asn Arg Gly Ser Cys Lys 340 345 350 Glu Thr Ser Leu Gly Phe Glu Cys Glu Cys Ser Pro Gly Trp Thr Gly 355 360 365 Pro Thr Cys Ser Thr Asn Ile Asp Asp Cys Ser Pro Asn Asn Cys Ser 370 380 His Gly Gly Thr Cys Gln Asp Leu Val Asn Gly Phe Lys Cys Val Cys 385 390 395 400 Pro Pro Gln Trp Thr Gly Lys Thr Cys Gln Leu Asp Ala Asn Glu Cys 405 410 415 Glu Ala Lys Pro Cys Val Asn Ala Lys Ser Cys Lys Asn Leu Ile Ala 420 425 430 Ser Tyr Tyr Cys Asp Cys Leu Pro Gly Trp Met Gly Gln Asn Cys Asp 435 440 445 Ile Asn Ile Asn Asp Cys Leu Gly Gln Cys Gln Asn Asp Ala Ser Cys 450 460 Arg Asp Leu Val Asn Gly Tyr Arg Cys Ile Cys Pro Pro Gly Tyr Ala 465 470 475 480 Gly Asp His Cys Glu Arg Asp Ile Asp Glu Cys Ala Ser Asn Pro Cys 485 490 495 Leu Asn Gly Gly His Cys Gln Asn Glu Ile Asn Arg Phe Gln Cys Leu 500 510 Cys Pro Thr Gly Phe Ser Gly Asn Leu Cys Gln Leu Asp Ile Asp Tyr 515 520 525 Cys Glu Pro Asn Pro Cys Gln Asn Gly Ala Gln Cys Tyr Asn Arg Ala 530 540 Ser Asp Tyr Phe Cys Lys Cys Pro Glu Asp Tyr Glu Gly Lys Asn Cys 545 550 555 560 Ser His Leu Lys Asp His Cys Arg Thr Thr Pro Cys Glu Val Ile Asp 565 570 575 Ser Cys Thr Val Ala Met Ala Ser Asn Asp Thr Pro Glu Gly Val Arg 580 585 590 Tyr Ile Ser Ser Asn Val Cys Gly Pro His Gly Lys Cys Lys Ser Gln 595 600 605 Ser Gly Gly Lys Phe Thr Cys Asp Cys Asn Lys Gly Phe Thr Gly Thr 610 620 Tyr Cys His Glu Asn Ile Asn Asp Cys Glu Ser Asn Pro Cys Arg Asn

625 630 635 640 Gly Gly Thr Cys Ile Asp Gly Val Asn Ser Tyr Lys Cys Ile Cys Ser 645 650 655 Asp Gly Trp Glu Gly Ala Tyr Cys Glu Thr Asn Ile Asn Asp Cys Ser 660 670 Gln Asn Pro Cys His Asn Gly Gly Thr Cys Arg Asp Leu Val Asn Asp 675 680 685 Phe Tyr Cys Asp Cys Lys Asn Gly Trp Lys Gly Lys Thr Cys His Ser 690 695 700 Arg Asp Ser Gln Cys Asp Glu Ala Thr Cys Asn Asn Gly Gly Thr Cys 705 710 715 720 Tyr Asp Glu Gly Asp Ala Phe Lys Cys Met Cys Pro Gly Gly Trp Glu 725 730 735 Gly Thr Thr Cys Asn Ile Ala Arg Asn Ser Ser Cys Leu Pro Asn Pro 740 745 750 Cys His Asn Gly Gly Thr Cys Val Val Asn Gly Glu Ser Phe Thr Cys 755 760 765 Val Cys Lys Glu Gly Trp Glu Gly Pro Ile Cys Ala Gln Asn Thr Asn 770 780 Asp Cys Ser Pro His Pro Cys Tyr Asn Ser Gly Thr Cys Val Asp Gly 785 790 795 800 Asp Asn Trp Tyr Arg Cys Glu Cys Ala Pro Gly Phe Ala Gly Pro Asp 805 810 815 Cys Arg Ile Asn Ile Asn Glu Cys Gln Ser Ser Pro Cys Ala Phe Gly 820 825 830 Ala Thr Cys Val Asp Glu Ile Asn Gly Tyr Arg Cys Val Cys Pro Pro 835 840 845 Gly His Ser Gly Ala Lys Cys Gln Glu Val Ser Gly Arg Pro Cys Ile 850 855 860 Thr Met Gly Ser Val Ile Pro Asp Gly Ala Lys Trp Asp Asp Cys 865 870 875 880 Asn Thr Cys Gln Cys Leu Asn Gly Arg Ile Ala Cys Ser Lys Val Trp 885 890 895 Cys Gly Pro Arg Pro Cys Leu Leu His Lys Gly His Ser Glu Cys Pro 900 905 910 Ser Gly Gln Ser Cys Ile Pro Ile Leu Asp Asp Gln Cys Phe Val His 915 920 925 Pro Cys Thr Gly Val Gly Glu Cys Arg Ser Ser Ser Leu Gln Pro Val 930 935 940 Lys Thr Lys Cys Thr Ser Asp Ser Tyr Tyr Gln Asp Asn Cys Ala Asn 945 950 955 960 Ile Thr Phe Thr Phe Asn Lys Glu Met Met Ser Pro Gly Leu Thr Thr 965 970 975

Glu His Ile Cys Ser Glu Leu Arg Asn Leu Asn Ile Leu Lys Asn Val 980 985 990

Ser Ala Glu Tyr Ser Ile Tyr Ile Ala Cys Glu Pro Ser Pro Ser Ala 995 1000 1005

Asn Asn Glu Ile His Val Ala Ile Ser Ala Glu Asp Ile Arg Asp 1010 1015 1020

Asp Gly Asn Pro Ile Lys Glu Ile Thr Asp Lys Ile Ile Asp Leu 1025 1030 1035

Val Ser Lys Arg Asp Gly Asn Ser Ser Leu Ile Ala Ala Val Ala 1040 1045 1050

Glu Val Arg Val Gln Arg Arg Pro Leu Lys Asn Arg Thr Asp Phe 1055 1060 1065

Leu Val Pro Leu Leu Ser Ser Val Leu Thr Val Ala Trp Ile Cys 1070 1075 1080

Cys Leu Val Thr Ala Phe Tyr Trp Cys Leu Arg Lys Arg Arg Lys 1085 1090 1095

Pro Gly Ser His Thr His Ser Ala Ser Glu Asp Asn Thr Thr Asn 1100 1105 1110

His Gly Ala Asn Thr Val Pro Ile Lys Asp Tyr Glu Asn Lys Asn 1130 1135 1140

Ser Lys Met Ser Lys Ile Arg Thr His Asn Ser Glu Val Glu Glu 1145 1150 1155

Asp Asp Met Asp Lys His Gln Gln Lys Ala Arg Phe Ala Lys Gln 1160 1170

Pro Ala Tyr Thr Leu Val Asp Arg Glu Glu Lys Pro Pro Asn Gly 1175 1180 1185

Thr Pro Thr Lys His Pro Asn Trp Thr Asn Lys Gln Asp Asn Arg 1190 1195 1200

Asp Leu Glu Ser Ala Gln Ser Leu Asn Arg Met Glu Tyr Ile Val 1205 1210 1215

<210> 38

<211> 1238

<212> PRT

<213> Homo sapiens

<400> 38

Met Arg Ala Gln Gly Arg Gly Arg Leu Pro Arg Arg Leu Leu Leu 1 5 10 15

Leu Ala Leu Trp Val Gln Ala Ala Arg Pro Met Gly Tyr Phe Glu Leu 20 25 30 Gln Leu Ser Ala Leu Arg Asn Val Asn Gly Glu Leu Leu Ser Gly Ala 35 40 45 Cys Cys Asp Gly Asp Gly Arg Thr Thr Arg Ala Gly Gly Cys Gly His 50 60 Asp Glu Cys Asp Thr Tyr Val Arg Val Cys Leu Lys Glu Tyr Gln Ala 65 70 75 80 Lys Val Thr Pro Thr Gly Pro Cys Ser Tyr Gly His Gly Ala Thr Pro 85 90 95 Val Leu Gly Gly Asn Ser Phe Tyr Leu Pro Pro Ala Gly Ala Ala Gly 100 105 110 Asp Arg Ala Arg Ala Arg Ala Gly Gly Asp Gln Asp Pro Gly 115 120 125 Leu Val Val Ile Pro Phe Gln Phe Ala Trp Pro Arg Ser Phe Thr Leu 130 140 Ile Val Glu Ala Trp Asp Trp Asp Asn Asp Thr Thr Pro Asn Glu Glu 145 150 155 160 Leu Leu Ile Glu Arg Val Ser His Ala Gly Met Ile Asn Pro Glu Asp 165 170 175 Arg Trp Lys Ser Leu His Phe Ser Gly His Val Ala His Leu Glu Leu 180 185 190 Gln Ile Arg Val Arg Cys Asp Glu Asn Tyr Tyr Ser Ala Thr Cys Asn 195 200 205 Lys Phe Cys Arg Pro Arg Asn Asp Phe Phe Gly His Tyr Thr Cys Asp 210 215 220 Gln Tyr Gly Asn Lys Ala Cys Met Asp Gly Trp Met Gly Lys Glu Cys 225 230 235 240 Lys Glu Ala Val Cys Lys Gln Gly Cys Asn Leu Leu His Gly Gly Cys 245 250 255 Thr Val Pro Gly Glu Cys Arg Cys Ser Tyr Gly Trp Gln Gly Arg Phe 260 265 270 Cys Asp Glu Cys Val Pro Tyr Pro Gly Cys Val His Gly Ser Cys Val 275 280 285 Glu Pro Trp Gln Cys Asn Cys Glu Thr Asn Trp Gly Gly Leu Leu Cys 290 295 300 Asp Lys Asp Leu Asn Tyr Cys Gly Ser His His Pro Cys Thr Asn Gly 305 310 315 320 Gly Thr Cys Ile Asn Ala Glu Pro Asp Gln Tyr Arg Cys Thr Cys Pro 325 330 335 Asp Gly Tyr Ser Gly Arg Asn Cys Glu Lys Ala Glu His Ala Cys Thr 340 345 350 Ser Asn Pro Cys Ala Asn Gly Gly Ser Cys His Glu Val Pro Ser Gly 355 360 365 Phe Glu Cys His Cys Pro Ser Gly Trp Ser Gly Pro Thr Cys Ala Leu 370

380

Asp Ile Asp Glu Cys Ala Ser Asn Pro Cys Ala Ala Gly Gly Thr Cys 385 390 395 400 Val Asp Gln Val Asp Gly Phe Glu Cys Ile Cys Pro Glu Gln Trp Val 405 410 415 Gly Ala Thr Cys Gln Leu Asp Ala Asn Glu Cys Glu Gly Lys Pro Cys 420 425 430 Leu Asn Ala Phe Ser Cys Lys Asn Leu Ile Gly Gly Tyr Tyr Cys Asp 435 440 445 Cys Ile Pro Gly Trp Lys Gly Ile Asn Cys His Ile Asn Val Asn Asp 450 455 460 Cys Arg Gly Gln Cys Gln His Gly Gly Thr Cys Lys Asp Leu Val Asn 465 470 475 480 Gly Tyr Gln Cys Val Cys Pro Arg Gly Phe Gly Gly Arg His Cys Glu 485 490 495 Leu Glu Arg Asp Lys Cys Ala Ser Ser Pro Cys His Ser Gly Gly Leu 500 510 Cys Glu Asp Leu Ala Asp Gly Phe His Cys His Cys Pro Gln Gly Phe 515 520 525 Ser Gly Pro Leu Cys Glu Val Asp Val Asp Leu Cys Glu Pro Ser Pro 530 540 Cys Arg Asn Gly Ala Arg Cys Tyr Asn Leu Glu Gly Asp Tyr Tyr Cys 545 550 555 560 Ala Cys Pro Asp Asp Phe Gly Gly Lys Asn Cys Ser Val Pro Arg Glu 565 570 575 Pro Cys Pro Gly Gly Ala Cys Arg Val Ile Asp Gly Cys Gly Ser Asp 580 585 590 Ala Gly Pro Gly Met Pro Gly Thr Ala Ala Ser Gly Val Cys Gly Pro 595 600 605 His Gly Arg Cys Val Ser Gln Pro Gly Gly Asn Phe Ser Cys Ile Cys 610 620 Asp Ser Gly Phe Thr Gly Thr Tyr Cys His Glu Asn Ile Asp Asp Cys 625 630 635 Leu Gly Gln Pro Cys Arg Asn Gly Gly Thr Cys Ile Asp Glu Val Asp 645 650 655 Ala Phe Arg Cys Phe Cys Pro Ser Gly Trp Glu Gly Glu Leu Cys Asp 660 670 Thr Asn Pro Asn Asp Cys Leu Pro Asp Pro Cys His Ser Arg Gly Arg 675 680 685 Cys Tyr Asp Leu Val Asn Asp Phe Tyr Cys Ala Cys Asp Asp Gly Trp 690 700 Lys Gly Lys Thr Cys His Ser Arg Glu Phe Gln Cys Asp Ala Tyr Thr 705 710 715 720

Cys Ser Asn Gly Gly Thr Cys Tyr Asp Ser Gly Asp Thr Phe Arg Cys
725 730 735 Ala Cys Pro Pro Gly Trp Lys Gly Ser Thr Cys Ala Val Ala Lys Asn 740 745 750 Ser Ser Cys Leu Pro Asn Pro Cys Val Asn Gly Gly Thr Cys Val Gly 755 760 765 Ser Gly Ala Ser Phe Ser Cys Ile Cys Arg Asp Gly Trp Glu Gly Arg 770 780 Thr Cys Thr His Asn Thr Asn Asp Cys Asn Pro Leu Pro Cys Tyr Asn 785 790 795 800 Gly Gly Ile Cys Val Asp Gly Val Asn Trp Phe Arg Cys Glu Cys Ala 805 810 815 Pro Gly Phe Ala Gly Pro Asp Cys Arg Ile Asn Ile Asp Glu Cys Gln 820 825 830 Ser Ser Pro Cys Ala Tyr Gly Ala Thr Cys Val Asp Glu Ile Asn Gly 835 840 Tyr Arg Cys Ser Cys Pro Pro Gly Arg Ala Gly Pro Arg Cys Gln Glu 850 855 860 Val Ile Gly Phe Gly Arg Ser Cys Trp Ser Arg Gly Thr Pro Phe Pro 865 870 875 880 His Gly Ser Ser Trp Val Glu Asp Cys Asn Ser Cys Arg Cys Leu Asp 885 890 895 Gly Arg Arg Asp Cys Ser Lys Val Trp Cys Gly Trp Lys Pro Cys Leu
900 905 910 Leu Ala Gly Gln Pro Glu Ala Leu Ser Ala Gln Cys Pro Leu Gly Gln 915 920 925 Arg Cys Leu Glu Lys Ala Pro Gly Gln Cys Leu Arg Pro Pro Cys Glu 930 935 940 Ala Trp Gly Glu Cys Gly Ala Glu Glu Pro Pro Ser Thr Pro Cys Leu 945 950 955 960 Pro Arg Ser Gly His Leu Asp Asn Cys Ala Arg Leu Thr Leu His 965 970 975 Phe Asn Arg Asp His Val Pro Gln Gly Thr Thr Val Gly Ala Ile Cys 980 985 990 Ser Gly Ile Arg Ser Leu Pro Ala Thr Arg Ala Val Ala Arg Asp Arg 995 1000 1005 Leu Leu Val Leu Leu Cys Asp Arg Ala Ser Ser Gly Ala Ser Ala 1010 1015 1020 Val Glu Val Ala Val Ser Phe Ser Pro Ala Arg Asp Leu Pro Asp 1025 1030 1035 Ser Ser Leu Ile Gln Gly Ala Ala His Ala Ile Val Ala Ala Ile 1050 Thr Gln_ Arg Gly Asn Ser Ser_ Leu Leu Leu Ala Val_ Thr Glu Val 1055 1060 1065

Lys Val Glu Thr Val Val Thr Gly Gly Ser Ser Thr Gly Leu Leu 1070 1080

Val Pro Val Leu Cys Gly Ala Phe Ser Val Leu Trp Leu Ala Cys 1085 1090 1095

Val Val Leu Cys Val Trp Trp Thr Arg Lys Arg Arg Lys Glu Arg 1100 1105 1110

Glu Arg Ser Arg Leu Pro Arg Glu Glu Ser Ala Asn Asn Gln Trp 1115 1120 1125

Ala Pro Leu Asn Pro Ile Arg Asn Pro Ile Glu Arg Pro Gly Gly 1130 1140

His Lys Asp Val Leu Tyr Gln Cys Lys Asn Phe Thr Pro Pro Pro 1145 1150 1155

Arg Arg Ala Asp Glu Ala Leu Pro Gly Pro Ala Gly His Ala Ala 1160 1170

Val Arg Glu Asp Glu Glu Asp Glu Asp Leu Gly Arg Gly Glu Glu 1175 1180 1185

Asp Ser Leu Glu Ala Glu Lys Phe Leu Ser His Lys Phe Thr Lys 1190 1200

Asp Pro Gly Arg Ser Pro Gly Arg Pro Ala His Trp Ala Ser Gly 1205 1215

Pro Lys Val Asp Asn Arg Ala Val Arg Ser Ile Asn Glu Ala Arg 1220 1230

Tyr Ala Gly Lys Glu 1235

<210> 39

<211> 2556

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<222> (891)..(891)

<223> X is any amino acid

<400> 39

Met Pro Pro Leu Leu Ala Pro Leu Leu Cys Leu Ala Leu Leu Pro Ala 10 15

Leu Ala Ala Arg Gly Pro Arg Cys Ser Gln Pro Gly Glu Thr Cys Leu 20 25 30

Asn Gly Gly Lys Cys Glu Ala Ala Asn Gly Thr Glu Ala Cys Val Cys 35 40 45 Gly Gly Ala Phe Val Gly Pro Arg Cys Gln Asp Pro Asn Pro Cys Leu 50 60 Ser Thr Pro Cys Lys Asn Ala Gly Thr Cys His Val Val Asp Arg Arg 65 70 75 80 Gly Val Ala Asp Tyr Ala Cys Ser Cys Ala Leu Gly Phe Ser Gly Pro 85 90 95 Leu Cys Leu Thr Pro Leu Asp Asn Ala Cys Leu Thr Asn Pro Cys Arg $100 \hspace{1cm} 105 \hspace{1cm} 110$ Asn Gly Gly Thr Cys Asp Leu Leu Thr Leu Thr Glu Tyr Lys Cys Arg 115 120 125 Cys Pro Pro Gly Trp Ser Gly Lys Ser Cys Gln Gln Ala Asp Pro Cys 130 140 Ala Ser Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Pro Phe Glu Ala 145 150 155 160 Ser Tyr Ile Cys His Cys Pro Pro Ser Phe His Gly Pro Thr Cys Arg 165 170 175 Gln Asp Val Asn Glu Cys Gly Gln Lys Pro Arg Leu Cys Arg His Gly 180 185 190 Gly Thr Cys His Asn Glu Val Gly Ser Tyr Arg Cys Val Cys Arg Ala 195 200 205 Thr His Thr Gly Pro Asn Cys Glu Arg Pro Tyr Val Pro Cys Ser Pro 210 215 220 Ser Pro Cys Gln Asn Gly Gly Thr Cys Arg Pro Thr Gly Asp Val Thr 225 230 235 240 His Glu Cys Ala Cys Leu Pro Gly Phe Thr Gly Gln Asn Cys Glu Glu 245 250 255 Asn Ile Asp Asp Cys Pro Gly Asn Asn Cys Lys Asn Gly Gly Ala Cys 260 265 270 Val Asp Gly Val Asn Thr Tyr Asn Cys Pro Cys Pro Pro Glu Trp Thr 275 280 285 Gly Gln Tyr Cys Thr Glu Asp Val Asp Glu Cys Gln Leu Met Pro Asn 290 295 300 Ala Cys Gln Asn Gly Gly Thr Cys His Asn Thr His Gly Gly Tyr Asn 305 310 315 320 Cys Val Cys Val Asn Gly Trp Thr Gly Glu Asp Cys Ser Glu Asn Ile 325 330 335 Asp Asp Cys Ala Ser Ala Ala Cys Phe His Gly Ala Thr Cys His Asp 340 345 350 Arg Val Ala Ser Phe Tyr Cys Glu Cys Pro His Gly Arg Thr Gly Leu 355 360 365 Leu Cys His Leu Asn Asp Ala Cys Ile Ser Asn Pro Cys Asn Glu Gly 370 380

Ser Asn Cys Asp Thr Asn Pro Val Asn Gly Lys Ala Ile Cys Thr Cys 385 390 395 400 Pro Ser Gly Tyr Thr Gly Pro Ala Cys Ser Gln Asp Val Asp Glu Cys 405 410 415 Ser Leu Gly Ala Asn Pro Cys Glu His Ala Gly Lys Cys Ile Asn Thr 420 425 430 Leu Gly Ser Phe Glu Cys Gln Cys Leu Gln Gly Tyr Thr Gly Pro Arg 435 440 445 Cys Glu Ile Asp Val Asn Glu Cys Val Ser Asn Pro Cys Gln Asn Asp 450 460 Ala Thr Cys Leu Asp Gln Ile Gly Glu Phe Gln Cys Met Cys Met Pro 465 470 475 480 Gly Tyr Glu Gly Val His Cys Glu Val Asn Thr Asp Glu Cys Ala Ser 485 490 495 Ser Pro Cys Leu His Asn Gly Arg Cys Leu Asp Lys Ile Asn Glu Phe 500 510 Gln Cys Glu Cys Pro Thr Gly Phe Thr Gly His Leu Cys Gln Tyr Asp 515 520 525 Val Asp Glu Cys Ala Ser Thr Pro Cys Lys Asn Gly Ala Lys Cys Leu 530 540 Asp Gly Pro Asn Thr Tyr Thr Cys Val Cys Thr Glu Gly Tyr Thr Gly 545 555 560 Thr His Cys Glu Val Asp Ile Asp Glu Cys Asp Pro Asp Pro Cys His 565 570 575 Tyr Gly Ser Cys Lys Asp Gly Val Ala Thr Phe Thr Cys Leu Cys Arg 580 585 590 Pro Gly Tyr Thr Gly His His Cys Glu Thr Asn Ile Asn Glu Cys Ser 595 600 605 Ser Gln Pro Cys Arg Leu Arg Gly Thr Cys Gln Asp Pro Asp Asn Ala 610 615 620 Tyr Leu Cys Phe Cys Leu Lys Gly Thr Thr Gly Pro Asn Cys Glu Ile 625 630 635 640 Asn Leu Asp Asp Cys Ala Ser Ser Pro Cys Asp Ser Gly Thr Cys Leu 645 650 655 Asp Lys Ile Asp Gly Tyr Glu Cys Ala Cys Glu Pro Gly Tyr Thr Gly 660 665 670 Ser Met Cys Asn Ser Asn Ile Asp Glu Cys Ala Gly Asn Pro Cys His 675 680 685 Asn Gly Gly Thr Cys Glu Asp Gly Ile Asn Gly Phe Thr Cys Arg Cys 690 700 Pro Glu Gly Tyr His Asp Pro Thr Cys Leu Ser Glu Val Asn Glu Cys 705 710 715 720 Asn Ser Asn Pro Cys Val His Gly Ala Cys Arg Asp Ser Leu Asn Gly

Tyr Lys Cys Asp Cys Asp Pro Gly Trp Ser Gly Thr Asn Cys Asp Ile 740 745 750 Asn Asn Glu Cys Glu Ser Asn Pro Cys Val Asn Gly Gly Thr Cys 755 760 765 Lys Asp Met Thr Ser Gly Ile Val Cys Thr Cys Arg Glu Gly Phe Ser 770 775 780 Gly Pro Asn Cys Gln Thr Asn Ile Asn Glu Cys Ala Ser Asn Pro Cys 785 790 795 800 Leu Asn Lys Gly Thr Cys Ile Asp Asp Val Ala Gly Tyr Lys Cys Asn 805 810 815 Cys Leu Leu Pro Tyr Thr Gly Ala Thr Cys Glu Val Val Leu Ala Pro 820 825 830 Cys Ala Pro Ser Pro Cys Arg Asn Gly Glu Cys Arg Gln Ser Glu 835 840 845 Asp Tyr Glu Ser Phe Ser Cys Val Cys Pro Thr Ala Gly Ala Lys Gly 850 860 Gln Thr Cys Glu Val Asp Ile Asn Glu Cys Val Leu Ser Pro Cys Arg 865 870 875 880 His Gly Ala Ser Cys Gln Asn Thr His Gly Xaa Tyr Arg Cys His Cys 885 890 895 Gln Ala Gly Tyr Ser Gly Arg Asn Cys Glu Thr Asp Ile Asp Asp Cys 900 905 910 Arg Pro Asn Pro Cys His Asn Gly Gly Ser Cys Thr Asp Gly Ile Asn 915 920 925 Thr Ala Phe Cys Asp Cys Leu Pro Gly Phe Arg Gly Thr Phe Cys Glu 930 935 940 Glu Asp Ile Asn Glu Cys Ala Ser Asp Pro Cys Arg Asn Gly Ala Asn 945 950 955 960 Cys Thr Asp Cys Val Asp Ser Tyr Thr Cys Thr Cys Pro Ala Gly Phe 965 970 975 Ser Gly Ile His Cys Glu Asn Asn Thr Pro Asp Cys Thr Glu Ser Ser 980 985 990 Cys Phe Asn Gly Gly Thr Cys Val Asp Gly Ile Asn Ser Phe Thr Cys 995 1000 1005 Leu Cys Pro Pro Gly Phe Thr Gly Ser Tyr Cys Gln His Val Val 1010 1015 1020 Asn Glu Cys Asp Ser Arg Pro Cys Leu Leu Gly Gly Thr Cys Gln 1025 1030 Asp Gly Arg Gly Leu His Arg Cys Thr Cys Pro Gln Gly Tyr Thr 1040 1045 1050 Gly Pro Asn Cys Gln Asn Leu Val His Trp Cys Asp Ser Ser Pro 1055 1060 1065

Cys Lys Asn Gly Gly Lys Cys Trp Gln Thr His Thr Gln Tyr Arg 1070 1075 1080 Cys Glu Cys Pro Ser Gly Trp Thr Gly Leu Tyr Cys Asp Val Pro 1085 1090 1095 Ser Val Ser Cys Glu Val Ala Ala Gln Arg Gln Gly Val Asp Val Leu Cys Gln His Gly Gly Leu Cys Val Asp Ala Gly Asn 1120 1125 Thr His His Cys Arg Cys Gln Ala Gly Tyr Thr Gly Ser Tyr Cys 1130 1140 Leu Val Asp Glu Cys Ser Pro Ser Pro Cys Gln Asn Gly 1150 1155 Glu Asp Ala Thr Cys Thr Asp Tyr Leu Gly Gly Tyr Ser Cys Lys Cys Val 1160 1165 1170 Ala Gly Tyr His Gly Val Asn Cys Ser Glu Glu Ile Asp Glu Cys 1180 Leu Ser His Pro Cys Gln Asn Gly Gly Thr Cys Leu Asp Leu Pro 1190 1195 Asn Thr Tyr Lys Cys Ser Cys Pro Arg Gly Thr Gln Gly Val His 1205 1210 1215 Ile Asn Val Asp Asp Cys Asn Pro Pro Val Asp Pro Val 1225 1230 Ser Arg Ser Pro Lys Cys Phe Asn Asn Gly Thr Cys Val Asp Gln 1235 1240 1245 Val Gly Gly Tyr Ser Cys Thr Cys Pro Pro Gly Phe Val Gly Glu 1260 Arg Cys Glu Gly Asp Val Asn Glu Cys Leu Ser Asn Pro Cys Asp 1265 1270 Ala Arg Gly Thr Gln Asn Cys Val Gln Arg Val Asn Asp Phe His 1280 1285 1290 1290 Cys Glu Cys Arg Ala Gly His Thr Gly Arg Arg Cys Glu Ser Val 1295 1300 1305 1300 Ile Asn Gly Cys Lys Gly Lys Pro Cys Lys Asn Gly Gly Thr Cys 1310 1315 1320 Ala Ser Asn Thr Ala Arg Gly Phe Ile Cys Lys Cys Pro 1330 1335 Ala Val Phe Glu Gly Ala Thr Cys Glu Asn Asp Ala Arg Thr Cys Ala Gly 1345 1350 Leu Arg Cys Leu Asn Gly Gly Thr Cys Ile Ser Gly Pro 1360 Pro Thr Cys Leu Cys Leu Gly Pro Phe Thr Gly Pro Glu 1375 1380 Arg Ser 1370 1380 Phe Pro Ala Ser Ser Pro Cys Leu Gly Gly Asn Pro Cys 1390 1395 Cys Gln 1385

Tyr Asn Gln Gly Thr Cys Glu Pro Thr Ser Glu Ser Pro Phe Tyr Arg Cys_ Leu Cys Pro Ala Lys_ Phe Asn Gly Leu Leu Cys His Ile Leu Asp Tyr Ser Phe Gly Gly Gly Ala Gly Arg Asp Ile Pro Pro 1430 1440 Pro Leu Ile Glu Glu Ala Cys Glu Leu Pro Glu Cys Gln Glu Asp 1445 1450 1455 1445 Ala Gly Asn Lys Val Cys Ser Leu Gln Cys Asn Asn His Ala Cys 1465 1470 Gly Trp Asp Gly Gly Asp Cys Ser Leu Asn Phe Asn Asp Pro Trp 1480 1485 Lys Asn Cys Thr Gln Ser Leu Gln Cys Trp Lys Tyr Phe Ser Asp 1490 1495 1500 Gly His Cys Asp Ser Gln Cys Asn Ser Ala Gly Cys Leu Phe Asp 1505 1510 1515 Gly Phe Asp Cys Gln Arg Ala Glu Gly Gln Cys Asn Pro Leu Tyr 1530 Asp Gln Tyr Cys Lys Asp His Phe Ser Asp Gly His Cys Asp Gln 1540 1545 Gly Cys Asn Ser Ala Glu Cys Glu Trp Asp Gly Leu Asp Cys Ala Glu His Val Pro Glu Arg Leu Ala Ala Gly Thr Leu Val Val Val 1565 1570 Val Leu Met Pro Pro Glu Gln Leu Arg Asn Ser Ser Phe His Phe 1580 1585 1590 Leu Arg_ Glu Leu Ser Arg Val Leu His Thr Asn Val Val Phe Lys 1600 1605 Arg Asp Ala His Gly Gln Gln Met Ile Phe Pro Tyr Tyr Gly Arg 1620 1610 1615 Glu Glu Leu Arg Lys His Pro Ile Lys Arg Ala Ala Glu Gly 1625 1630 1635 Trp Ala Ala Pro Asp Ala Leu Leu Gly Gln Val Lys Ala Ser Leu 1640 1645 Leu Pro Gly Gly Ser Glu Gly Gly Arg Arg Arg Glu Leu Asp 1660 1665 Pro Met Asp Val Arg Gly Ser Ile Val Tyr Leu Glu Ile Asp Asn 1670 1675 1680 Arg Gln_Cys Val Gln Ala Ser_Ser Gln Cys Phe Gln_Ser Ala Thr 1690 1695 Asp Val Ala Ala Phe Leu Gly Ala Leu Ala Ser Leu Gly Ser Leu 1700 1710 Asn Ile Pro Tyr Lys Ile Glu Ala Val Gln Ser Glu Thr Val Glu

Pro Pro Pro Ala Gln Leu His Phe Met Tyr Val Ala Ala Ala Ala Phe Val Leu Leu Phe Phe Val Gly Cys Gly Val Leu Leu Ser Arg Lys Arg Arg Arg Gln His Gly Gln Leu Trp Phe Pro Glu Gly Phe Lys Val Ser Glu Ala Ser Lys Lys Lys Arg Arg Glu Pro Leu 1775 1780 1785 Gly Glu Asp Ser Val Gly Leu Lys Pro Leu Lys Asn Ala Ser Asp Gly Ala Leu Met Asp Asp Asn Gln Asn Glu Trp Gly Asp Glu Asp 1805 1810 1815 Leu Glu Thr Lys Lys Phe Arg Phe Glu Glu Pro Val Val Leu Pro 25 Asp Leu Asp Asp Gln Thr Asp His Arg Gln Trp Thr Gln Gln His Leu Asp Ala Ala Asp Leu Arg Met Ser Ala Met Ala Pro Thr Pro Pro Gln Gly Glu Val Asp Ala Asp Cys Met Asp Val Asn Val Arg Gly Pro Asp Gly Phe Thr Pro Leu Met Ile Ala Ser Cys Ser Gly Gly Gly Leu Glu Thr Gly Asn Ser Glu Glu Glu Glu Asp Ala Pro Ala Val Ile Ser Asp Phe Ile Tyr Gln Gly Ala Ser Leu His Asn Gln Thr Asp Arg Thr Gly Glu Thr Ala Leu His Leu Ala Ala Arg Tyr Ser Arg Ser Asp Ala Ala Lys Arg Leu Leu Glu Ala Ser Ala Asp Ala Asn Ile Gln Asp Asn Met Gly Arg Thr Pro Leu His Ala Ala Val Ser Ala Asp Ala Gln Gly Val Phe Gln Ile Leu Ile Arg Ala Thr Asp Leu Asp Ala Arg Met His Asp Gly Thr Thr 1990 1995 Asn Arg Pro Leu Ile Leu Ala Ala Arg Leu Ala Val Glu Gly Met Leu Glu 20<u>0</u>5 Asp Leu Ile Asn Ser His Ala Asp Val Asn Ala Val Asp Asp Leu Ser Ala Leu His Trp Ala Ala Ala Val Asn Asn Val Asp

Ala Ala Val Val Leu Leu Lys Asn Gly Ala Asn Lys Asp Met Gln 2045 2055 Asn Asn Arg Glu Glu Thr Pro Leu Phe Leu Ala Ala Arg Glu Gly 2065 2070 2060 Ser Tyr Glu Thr Ala Lys Val Leu Leu Asp His Phe Ala Asn Arg 2080 2085 Asp Ile Thr Asp His Met Asp Arg Leu Pro Arg Asp Ile Ala Gln 2090 2100 2100 Glu Arg Met His His Asp Ile Val Arg Leu Leu Asp Glu Tyr Asn 2105 2115 Leu Val Arg Ser Pro Gln Leu His Gly Ala Pro Leu Gly Gly Thr 2120 2125 Leu Ser Pro Pro Leu Cys Ser Pro Asn Gly Tyr Leu Gly 2140 2145 Pro Thr Ser Leu Lys Pro Gly Val Gln Gly Lys Lys Val Arg Lys Pro Ser 2155 2150 Ser Lys Gly Leu Ala Cys Gly Ser Lys Glu Ala Lys Asp Leu Lys 2165 2170 2175 Ala Arg Arg Lys Lys Ser Gln Asp Gly Lys Gly Cys Leu Leu Asp 2180 2185 2190 Ser Ser Gly Met Leu Ser Pro Val Asp Ser Leu Glu Ser Pro His 2200 2205 Gly Tyr Leu Ser Asp Val Ala Ser Pro Pro Leu Leu Pro Ser Pro 2215 2220 Phe Gln Gln Ser Pro Ser Val Pro Leu Asn His Leu Pro Gly Met 2235 2230 2225 Pro Asp Thr His Leu Gly Ile Gly His Leu Asn Val Ala Ala Lys Pro Glu Met Ala Ala Leu Gly Gly Gly Gly Arg Leu Ala Phe Glu 2255 2260 2265 Pro Pro Arg Leu Ser His Leu Pro Val Ala Ser Gly Thr 2270 2280 2275 Ser Thr Val Leu Gly Ser Ser Ser Gly Gly Ala Leu Asn Phe Thr 2290 2295 Val Gly Gly Ser Thr Ser Leu Asn Gly Gln Cys Glu Trp Leu Ser Arg Leu Gln Ser Gly Met Val Pro Asn Gln Tyr Asn Pro Leu Arg 2315 2320 2325 Gly Ser Val Ala Pro Gly Pro Leu Ser Thr Gln Ala Pro Ser Leu 2335 2340 Gln His Gly Met Val Gly Pro Leu His Ser Ser Leu Ala Ala Ser 2350 2355 Ala Leu Ser Gln Met Met Ser Tyr Gln Gly Leu Pro Ser Thr Arg 2365 2360 2370

Leu Ala Thr Gln Pro His Leu Val Gln Thr Gln Gln Val Gln Pro 2375 2380 2385

Gln Asn Leu Gln Met Gln Gln Gln Asn Leu Gln Pro Ala Asn Ile 2390 2395 2400

Gln Gln Gln Ser Leu Gln Pro Pro Pro Pro Pro Gln Pro 2405 2410 2415

His Leu Gly Val Ser Ser Ala Ala Ser Gly His Leu Gly Arg Ser 2420 2425 2430

Phe Leu Ser Gly Glu Pro Ser Gln Ala Asp Val Gln Pro Leu Gly 2435 2440 2445

Pro Ser Ser Leu Ala Val His Thr Ile Leu Pro Gln Glu Ser Pro 2450 2455 2460

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Ala Ala Gln Phe Leu Thr Pro Pro Ser Gln His Ser Tyr Ser Ser 2480 2485 2490

Pro Val Asp Asn Thr Pro Ser His Gln Leu Gln Val Pro Glu His 2495 2500 2505

Pro Phe Leu Thr Pro Ser Pro Glu Ser Pro Asp Gln Trp Ser Ser 2510 2515 2520

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Leu Cys Cys Ala Ala Pro Ala His Ala Leu Gln Cys Arg Asp Gly Tyr 20 25 30

Glu Pro Cys Val Asn Glu Gly Met Cys Val Thr Tyr His Asn Gly Thr

Gly Tyr Cys Lys Cys Pro Glu Gly Phe Leu Gly Glu Tyr Cys Gln His 50 60

Arg Asp Pro Cys Glu Lys Asn Arg Cys Gln Asn Gly Gly Thr Cys Val

Ala Gln Ala Met Leu Gly Lys Ala Thr Cys Arg Cys Ala Ser Gly Phe 85 90 95 Thr Gly Glu Asp Cys Gln Tyr Ser Thr Ser His Pro Cys Phe Val Ser 100 105 110 Arg Pro Cys Leu Asn Gly Gly Thr Cys His Met Leu Ser Arg Asp Thr 115 120 125 Tyr Glu Cys Thr Cys Gln Val Gly Phe Thr Gly Lys Glu Cys Gln Trp 130 135 140 Thr Asp Ala Cys Leu Ser His Pro Cys Ala Asn Gly Ser Thr Cys Thr 145 150 155 160 Thr Val Ala Asn Gln Phe Ser Cys Lys Cys Leu Thr Gly Phe Thr Gly 165 170 175 Gln Lys Cys Glu Thr Asp Val Asn Glu Cys Asp Ile Pro Gly His Cys 180 185 190 Gln His Gly Gly Thr Cys Leu Asn Leu Pro Gly Ser Tyr Gln Cys Gln 195 200 205 Cys Pro Gln Gly Phe Thr Gly Gln Tyr Cys Asp Ser Leu Tyr Val Pro 210 220 Cys Ala Pro Ser Pro Cys Val Asn Gly Gly Thr Cys Arg Gln Thr Gly 225 230 235 240 Asp Phe Thr Phe Glu Cys Asn Cys Leu Pro Gly Phe Glu Gly Ser Thr 245 250 255 Cys Glu Arg Asn Ile Asp Asp Cys Pro Asn His Arg Cys Gln Asn Gly 260 265 270 Gly Val Cys Val Asp Gly Val Asn Thr Tyr Asn Cys Arg Cys Pro Pro 275 280 285 Gln Trp Thr Gly Gln Phe Cys Thr Glu Asp Val Asp Glu Cys Leu Leu 290 295 300 Gln Pro Asn Ala Cys Gln Asn Gly Gly Thr Cys Ala Asn Arg Asn Gly 305 310 315 320 Gly Tyr Gly Cys Val Cys Val Asn Gly Trp Ser Gly Asp Asp Cys Ser 325 330 335 Glu Asn Ile Asp Asp Cys Ala Phe Ala Ser Cys Thr Pro Gly Ser Thr 340 345 350 Cys Ile Asp Arg Val Ala Ser Phe Ser Cys Met Cys Pro Glu Gly Lys 355 360 365 Ala Gly Leu Leu Cys His Leu Asp Asp Ala Cys Ile Ser Asn Pro Cys 370 380 His Lys Gly Ala Leu Cys Asp Thr Asn Pro Leu Asn Gly Gln Tyr Ile 385 390 395 400 Cys Thr Cys Pro Gln Gly Tyr Lys Gly Ala Asp Cys Thr Glu Asp Val 405 410 415

Asp Glu Cys Ala Met Ala Asn Ser Asn Pro Cys Glu His Ala Gly Lys 420 425 430 Cys Val Asn Thr Asp Gly Ala Phe His Cys Glu Cys Leu Lys Gly Tyr 435 440 445 Ala Gly Pro Arg Cys Glu Met Asp Ile Asn Glu Cys His Ser Asp Pro 450 460 Cys Gln Asn Asp Ala Thr Cys Leu Asp Lys Ile Gly Gly Phe Thr Cys 465 470 475 480 Leu Cys Met Pro Gly Phe Lys Gly Val His Cys Glu Leu Glu Ile Asn 485 490 495 Glu Cys Gln Ser Asn Pro Cys Val Asn Asn Gly Gln Cys Val Asp Lys 500 505 510 Val Asn Arg Phe Gln Cys Leu Cys Pro Pro Gly Phe Thr Gly Pro Val 515 520 525 Cys Gln Ile Asp Ile Asp Asp Cys Ser Ser Thr Pro Cys Leu Asn Gly 530 540 Ala Lys Cys Ile Asp His Pro Asn Gly Tyr Glu Cys Gln Cys Ala Thr 545 550 555 560 Gly Phe Thr Gly Val Leu Cys Glu Glu Asn Ile Asp Asn Cys Asp Pro 565 570 575 Asp Pro Cys His His Gly Gln Cys Gln Asp Gly Ile Asp Ser Tyr Thr 580 585 590 Cys Ile Cys Asn Pro Gly Tyr Met Gly Ala Ile Cys Ser Asp Gln Ile 595 600 605 Glu Cys Tyr Ser Ser Pro Cys Leu Asn Asp Gly Arg Cys Ile Asp 610 620 Leu Val Asn Gly Tyr Gln Cys Asn Cys Gln Pro Gly Thr Ser Gly Val 625 630 635 640 Asn Cys Glu Ile Asn Phe Asp Asp Cys Ala Ser Asn Pro Cys Ile His 645 650 655 Gly Ile Cys Met Asp Gly Ile Asn Arg Tyr Ser Cys Val Cys Ser Pro 660 665 670 Gly Phe Thr Gly Gln Arg Cys Asn Ile Asp Ile Asp Glu Cys Ala Ser 675 680 685 Asn Pro Cys Arg Lys Gly Ala Thr Cys Ile Asn Gly Val Asn Gly Phe 690 695 700 Arg Cys Ile Cys Pro Glu Gly Pro His His Pro Ser Cys Tyr Ser Gln 705 710 715 720 Val Asn Glu Cys Leu Ser Asn Pro Cys Ile His Gly Asn Cys Thr Gly 725 730 735 Gly Leu Ser Gly Tyr Lys Cys Leu Cys Asp Ala Gly Trp Val Gly Ile 740 745 750 Asn Cys Glu Val Asp Lys Asn Glu Cys Leu Ser Asn Pro Cys Gln Asn 755 760 765

Gly Gly Thr Cys Asp Asn Leu Val Asn Gly Tyr Arg Cys Thr Cys Lys 770 780 Lys Gly Phe Lys Gly Tyr Asn Cys Gln Val Asn Ile Asp Glu Cys Ala 785 790 795 800 Ser Asn Pro Cys Leu Asn Gln Gly Thr Cys Phe Asp Asp Ile Ser Gly 805 810 815Tyr Thr Cys His Cys Val Leu Pro Tyr Thr Gly Lys Asn Cys Gln Thr 820 825 830 Val Leu Ala Pro Cys Ser Pro Asn Pro Cys Glu Asn Ala Ala Val Cys 835 840 845 Lys Glu Ser Pro Asn Phe Glu Ser Tyr Thr Cys Leu Cys Ala Pro Gly 850 860 Trp Gln Gly Gln Arg Cys Thr Ile Asp Ile Asp Glu Cys Ile Ser Lys 865 870 875 880 Pro Cys Met Asn His Gly Leu Cys His Asn Thr Gln Gly Ser Tyr Met 885 890 895 Cys Glu Cys Pro Pro Gly Phe Ser Gly Met Asp Cys Glu Glu Asp Ile 900 905 910 Asp Asp Cys Leu Ala Asn Pro Cys Gln Asn Gly Gly Ser Cys Met Asp 915 920 925 Gly Val Asn Thr Phe Ser Cys Leu Cys Leu Pro Gly Phe Thr Gly Asp 930 935 940 Lys Cys Gln Thr Asp Met Asn Glu Cys Leu Ser Glu Pro Cys Lys Asn 945 955 960 Gly Gly Thr Cys Ser Asp Tyr Val Asn Ser Tyr Thr Cys Lys Cys Gln $965 \hspace{1cm} 970 \hspace{1cm} 975$ Ala Gly Phe Asp Gly Val His Cys Glu Asn Asn Ile Asn Glu Cys Thr 980 985 990 Glu Ser Ser Cys Phe Asn Gly Gly Thr Cys Val Asp Gly Ile Asn Ser 995 1000 1005 Phe Ser Cys Leu Cys Pro Val Gly Phe Thr Gly Ser Phe Cys Leu 1010 1015 1020 1020 His Glu Ile Asn Glu Cys Ser Ser His Pro Cys Leu Asn Glu Gly Thr Cys Val Asp Gly Leu Gly Thr Tyr Arg Cys Ser Cys Pro Leu 1040 1045 1050 Gly Tyr Thr Gly Lys Asn Cys Gln Thr Leu Val Asn Leu Cys Ser 1055 1060 1065 1065 Arg Ser Pro Cys Lys Asn Lys Gly Thr Cys Val Gln Lys Lys Ala 1070 1075 1080 Glu Ser Gln Cys Leu Cys Pro Ser Gly Trp Ala Gly Ala Tyr Cys 1085 1090 1095 Asp Val Pro Asn Val Ser Cys Asp Ile Ala Ala Ser Arg Arg Gly

1100 1105 1110 Val Leu Val Glu His Leu Cys Gln His Ser Gly Val Cys Ile Asn 1115 Ala Gly Asn Thr His Tyr Cys Gln Cys Pro Leu Gly Tyr Thr Gly
1130 1140 1140 Ser Tyr Cys Glu Glu Gln Leu Asp Glu Cys Ala Ser Asn Pro Cys 1150 Gln His Gly Ala Thr Cys Ser Asp Phe Ile Gly Gly Tyr Arg Cys 1160 1165 1170 Glu Cys_ Val Pro Gly Tyr Gln Gly Val Asn Cys Glu Tyr Glu Val 1180 1185 Asp Glu Cys Gln Asn Gln Pro Cys Gln Asn Gly Gly Thr Cys Ile 1200 1190 Asp Leu Val Asn His Phe Lys Cys Ser Cys Pro Pro Gly Thr Arg 1205 1210 1215 Gly Leu Leu Cys Glu Glu Asn Ile Asp Asp Cys Ala Arg Gly Pro His Cys Leu Asn Gly Gly Gln Cys Met Asp Arg Ile Gly Gly Tyr 1240 Ser Cys Arg Cys Leu Pro Gly Phe Ala Gly Glu Arg Cys Glu Gly 1250 1260 Asp Ile Asn Glu Cys Leu Ser Asn Pro Cys Ser Ser Glu Gly Ser 1270 1275 Leu Asp Cys Ile Gln Leu Thr Asn Asp Tyr Leu Cys Val Cys Arg 1280 1285 Ser Ala Phe Thr Gly Arg His Cys Glu Thr Phe Val Asp Val Cys 1300 1305 1295 Met Pro Cys Leu Asn Gly Gly Thr Cys Ala Val Ala Ser 1310 1315 Asn Met Pro Asp Gly Phe Ile Cys Arg Cys Pro Pro Gly Phe Ser 1330 1335 Gly Ala Arg Cys Gln Ser Ser Cys Gly Gln Val Lys Cys Arg Lys 1340 1350 Gln Cys Val His Thr Ala Ser Gly Pro Arg Cys Phe Cys Gly Glu 1360 1365 Pro Arg Asp Cys Glu Ser Gly Cys Ala Ser Ser Pro Cys Pro Ser 1370 1380 Gln His Gly Gly Ser Cys His Pro Gln Arg Gln Pro Pro Tyr Tyr 1385 1390 1395 Ser Cys Gln Cys Ala Pro Pro Phe Ser Gly Ser Arg Cys Glu Leu 1410 1405 Tyr Thr Ala Pro Pro Ser Thr Pro Pro Ala Thr Cys Leu Ser Gln 1425 1420

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Tyr Cys Ala Asp Lys Ala Arg Asp Gly Val Cys Asp Glu Ala Cys 1430 1440 Asn Ser_ His Ala Cys Gln Trp_ Asp Gly Gly Asp Cys_ Ser Leu Thr Met Glu Asn Pro Trp Ala Asn Cys Ser Ser Pro Leu Pro Cys Trp Ile Asn Asn Gln Cys Asp Glu Leu Cys Asn Thr Val Glu Phe Asp Asn Phe Glu Cys Gln Gly Asn Ser Lys Thr Cys Cys Leu Asp Lys Tyr Cys Ala Asp His Phe Lys Asp Asn His Cys Asn Gln Gly Cys Asn Ser Glu Glu Cys Gly Trp Asp Gly Leu Asp Cys Ala Ala Asp Gln Pro Glu Asn Leu Ala Glu Gly Thr Leu Val 1535 1540 1545 Ile Val Val Leu Met Pro Pro Glu Gln Leu Leu Gln Asp Ala Arg Ser Phe Leu Arg Ala Leu Gly Thr Leu Leu His Thr Asn Leu Arg 1565 1570 1575 Arg Asp Ser Gln Gly Glu Leu Met Val Tyr Pro Tyr Tyr 1585 1590 Ile Lys Gly Glu Lys Ser Ala Ala Met Lys Lys Gln Arg Met Thr Arg Arg Pro Gly Glu Gln Glu Gln Glu Val Ala Gly Ser Lys Val Ser Leu Phe Leu Glu Ile Asp Asn Arg Gln Cys Val Gln Asp Ser Asp His Cys Phe Lys Asn Thr Asp Ala Ala Ala Leu Leu Ala Ser His Ala Ile Gln Gly Thr Leu Ser Tyr Pro Leu Val Ser Val Val Ser Glu Ser Leu Thr Pro Glu Arg Thr Gln Leu Leu Tyr Leu Leu Ala Val Ala Val Val Ile Ile Leu Phe Ile Ile Leu Leu Gly Val Ile Met Ala Lys Arg Lys Arg Lys His Gly Ser Leu Trp Leu Pro Glu Gly Phe Thr Leu Arg Arg Asp Ala Ser Asn His Lys Arg Arg Glu 1715 1720 1725 Pro Val Gly Gln Asp Ala Val Gly Leu Lys Asn Leu Ser Val Gln 1730 1740 Val Ser Glu Ala Asn Leu Ile Gly Thr Gly Thr Ser Glu His Trp

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Val Asp Asp Glu Gly Pro Gln Pro Lys Lys Val Lys Ala Glu Asp 1760 1765 1770 Glu Ala Leu Leu Ser Glu Glu Asp Asp Pro Ile Asp Arg Arg Pro 1775 1780 1785 Trp Thr Gln Gln His Leu Glu Ala Ala Asp Ile Arg Arg Thr Pro 18Ŏ0 Ser Leu Ala Leu Thr Pro Pro Gln Ala Glu Gln Glu Val Asp Val Leu Asp Val Asn Val Arg Gly Pro Asp Gly Cys Thr Pro Leu Met Leu Ala Ser Leu Arg Gly Gly Ser Ser Asp Leu Ser Asp Glu Asp Glu Asp Ala Glu Asp Ser Ser Ala Asn Ile Ile Thr Asp Leu Val Tyr Gln Gly Ala Ser Leu Gln Ala Gln Thr Asp Arg Thr Gly Glu Met Ala Leu His Leu Ala Ala Arg Tyr Ser Arg Ala Asp Ala Ala Leu Leu Asp Ala Gly Ala Asp Ala Asn Ala Gln Asp Asn 1900 1905 Met Gly Arg Cys Pro Leu His Ala Ala Val Ala Ala Asp Ala Gln Gly Val Phe Gln Ile Leu Ile Arg Asn Arg Val Thr Asp Leu Asp Ala Arg Met Asn Asp Gly Thr Thr Pro Leu Ile Leu Ala Ala Arg Leu Ala_ Val Glu Gly Met Val Ala Glu Leu Ile Asn_ Cys Gln Ala Asp Val Asn Ala Val Asp Asp His Gly Lys Ser Ala Leu His Trp 1970 1975 1980 Ala Ala Ala Val Asn Asn Val Glu Ala Thr Leu Leu Leu Leu Lys Asn Gly Ala Asn Arg Asp Met Gln Asp Asn Lys Glu Glu Thr Pro Leu Phe Leu Ala Ala Arg Glu Gly Ser Tyr Glu Ala Ala Lys Ile Leu Leu Asp His Phe Ala Asn Arg Asp Ile Thr Asp His Met Asp Arg Leu Pro Arg Asp Val Ala Arg Asp Arg Met His His Asp Ile Leu Leu Asp Glu Tyr Asn Val Thr Pro Ser Pro Pro Gly 2065 2070 Thr Val Leu Thr Ser Ala Leu Ser Pro Val Ile Cys Gly Pro Asn

Arg Ser Phe Leu Ser Leu Lys His Thr Pro Met Gly Lys Lys Ser Pro Ser Ala Lys Ser Thr Met Pro Thr Ser Leu Pro Asn Leu Ala Lys Glu Ala Lys Asp Ala Lys Gly Ser Arg Arg Lys Lys 2120 2130 Ser Glu Lys Val Gln Leu Ser Glu Ser Ser Val Thr Leu Ser Leu Ser Pro Val Asp Ser Leu Glu Ser Pro His Thr Tyr Val Ser Asp Thr Thr Ser Ser Pro Met Ile Thr Ser Pro Gly Ile Leu Gln Ala Ser Pro Asn Pro Met Leu Ala Thr Ala Ala Pro Pro Ala Pro Val His Ala Gln His Ala Leu Ser Phe Ser Asn Leu His Glu Met Gln Pro Leu Ala His Gly Ala Ser Thr Val Leu Pro Ser Val Ser Gln Ser His His Ile Val Ser Pro Gly Ser Gly Ser Ala Leu Leu Gly Ser Leu Ser Arg Leu His Pro Val Pro Val Pro Ala Asp Trp Met Asn Arg Met Glu Val Asn Glu Thr Gln Tyr Asn Glu Met Phe Gly Met Val Leu Ala Pro Ala Glu Gly Thr His Pro Gly Ile Ala Pro Gln Ser Arg Pro Pro Glu Gly Lys His Ile Thr Thr Pro Arg Glu Pro Leu Pro Pro Ile Val Thr Phe Gln Leu Ile Pro Lys Gly Ser Ile Ala Gln Pro Ala Gly Ala Pro Gln Pro Gln Ser Thr Cys Pro Pro Ala Val Ala Gly Pro Leu Pro Thr Met Tyr Gln Ile Pro Glu Met Ala Arg Leu Pro Ser Val Ala Phe Pro Thr Ala Met Met Pro Gln Gln Asp Gly Gln Val Ala Gln Thr Ile Leu Pro Ala Tyr His Pro Phe Pro Ala Ser Val Gly Lys Tyr Pro Thr Pro Pro Ser Ser Tyr Ala Ser Ser Asn Ala Ala Glu Arg Thr Pro Ser

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His Ser 2405 Gly His Leu Gln Gly Glu His Pro Tyr Leu Thr Pro Ser 2405 Glu Ser Pro Asp Gln Trp Ser Ser Ser Ser Ser Pro His Ser Ala Ser Asp Trp Ser Asp Val Thr Ser Pro Thr Pro 2445 Gly Gly Ala Gly Gly Gln Arg Gly Pro 2455 Gly Thr His Met Ser Glu Pro Pro 2465 Asn Met Gln Val Tyr Ala

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